2216-2222 (1990) and Badger et al., *J. Mol. Biol., 207,* pp. 163-174 (1989). Applicant traverses the rejection.

The Examiner attempts to show that applicant's invention is obvious by combining references. However, with respect to combining references to support an obviousness rejection, the law is clear:

> "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." In re Geiger, 2 U.S.P.Q.2d 1276, 1278 (Fed.Cir. 1987) (emphasis added).

None of the references cited by the Examiner teach, suggest or otherwise provide any incentive supporting their combination. Accordingly, the combination of the references by the Examiner is improper as the basis for a rejection under 35 U.S.C. § 103.

Park et al. reported that a change in the single $G^3.U^{70}$ base pair in the acceptor helix of $tRNA^{Ala}$ to $A^3.U^{70}$ prevented aminoacylation of $tRNA^{Ala}$ by alanyl-tRNA synthetase. In particular, at pH 7.5, Park et al. were unable to find evidence of either aminoacylation of the $A^3.U^{70}$ variant $tRNA^{Ala}$ or inhibition of aminoacylation of the $G^3.U^{70}$ wildtype $tRNA^{Ala}$ by the $A^3.U^{70}$ variant. However, at pH 5.5, Park et al. observed that the $A^3.U^{70}$ variant $tRNA^{Ala}$ did inhibit aminoacylation of the $G^3.U^{70}$ wildtype $tRNA^{Ala}$. Coincidentally, binding of the synthetase to the $A^3.U^{70}$ variant $tRNA^{Ala}$ was also observed. Thus, the $A^3.U^{70}$ variant $tRNA^{Ala}$

binds to the synthetase at pH 5.5, but cannot be aminoacylated, and for this reason the $A^3.U^{70}$ variant $tRNA^{Ala}$ inhibits aminoacylation of the $G^3.U^{70}$ wildtype $tRNA^{Ala}$.

In opening remarks, Park et al. refer to publications that established that the $G^3.U^{70}$ site on a $tRNA^{Ala}$ was found to be critical to ensuring that the cognate alanyl-tRNA synthetase accurately identifies the $tRNA^{Ala}$ for aminoacylation. However, nowhere does Park et al. teach, suggest, or contemplate the key aspect of applicant's invention, i.e., the design of compounds to bind and block a site in the minor groove of a particular RNA. Nowhere do Park et al. determine that the $G^3.U^{70}$ site is in the minor groove of $tRNA^{Ala}$. Applicant, alone, is the first to appreciate that the $G^3.U^{70}$ site is in the minor groove of the $tRNA^{Ala}$ and, therefore, is an example of the kind of RNA envisioned as a target for compounds designed according to applicant's method (see, e.g., page 17, lines 4 - 25). Lacking this feature of applicant's invention, the primary reference of Park et al. does not form the basis of an obviousness rejection of the claims.

The Examiner was also of the view that the reference by Endo et al. supports the rejection because Endo et al. "determined the three-dimensional structure surrounding the targeted site" on the ribosome which is cleaved by α-sarcin, and because "Endo et al. disclose the delivery of the drug to the

rRNA in a buffered solution". Applicant agrees that the three dimensional, or tertiary structure, of the molecule is necessary for the identification of structural features such as the minor groove. However, while Endo et al. used oligoribonucleotides to examine the primary (i.e., nucleotide sequence) and secondary structural features (i.e., a "stem", a "bulged" nucleotide, and a "loop") necessary for α-sarcin to recognize and cleave at a site on ribosomal RNA (see first full paragraph on page 2217; and Figs 1 - 9), no three-dimensional structure of the cleavage site was determined. In fact, in discussing experiments designed to study the GAGA tetranucleotide sequence of rRNA that is cleaved by α-sarcin, Endo et al. state that:

> "[w]e cannot be sure from these experiments that α-sarcin is appreciating the position or geometry of the tetranucleotide." See first three lines of text at page 2221. (emphasis added).

Thus, Endo et al. express doubt as to the importance of the tertiary structure to α-sarcin cleavage and, thereby, actually teach away from the key feature of applicant's invention, i.e., designing a compound to specifically bind at a site in the minor groove of a targeted RNA to inhibit the function of the RNA.

Regarding the Examiner's view that Endo et al. disclose delivery of α-sarcin to rRNA in a buffered solution, applicant notes that use of buffered solutions to carry out the *in vitro* experiments described by Endo et al. is routine and in no way

discloses the key feature of applicant's invention, i.e., designing compounds that bind specifically at a critical site in the minor groove of a targeted RNA. Indeed, applicant states in his application that a variety of systems to administer therapeutic compounds are well-known by the skilled practitioner (see page 40, line 15 - page 41, line 29). Accordingly, Endo et al. adds nothing to Park et al. to render applicant's invention obvious.

The Examiner was of the view that Badger et al. renders applicant's invention obvious on the basis that Badger et al. used x-ray crystallographic analysis of the three-dimensional structure of rhinovirus and drug-resistant mutants, and suggested that such analysis may permit the design of drugs. Applicant notes that Badger et al. refer to the x-ray analysis of mutant viral <u>proteins</u> (not RNA), which are involved in uncoating the virus in the cell and which have become resistant to the antiviral effects of a family of compounds. Badger et al. speculate that their studies may be extended in the future to permit the design of antiviral agents that inhibit uncoating over a wide or selected range of viruses (see page 164). However, the Badger et al. publication lacks any teaching or suggestion of methods to design compounds which bind at a critical site in and block the minor groove of a targeted RNA as disclosed in

applicant's invention. Accordingly, Badger et al. cannot cure the deficiencies of Park et al. and Badger et al.

The above comments make clear that even if it were proper to combine the references cited by the Examiner (and it is not), such a combination could not support a rejection under 35 U.S.C. § 103. Accordingly, applicant requests that the Examiner reconsider and withdraw the rejection of the claims.

Claims 1 and 3 - 19 stand rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's view, the specification is not enabling in that one skilled in the art would not know how to determine the critical site and the minor groove of an RNA, nor how to design drugs. The Examiner was of the view that such procedures are essential and, therefore, must be incorporated in detail into the specification. Applicant traverses the rejection.

Applicant's disclosure makes clear that, as of the filing date of this application, there were a variety of well-known techniques and methods available to the skilled practitioner to determine the critical site and minor groove in an RNA molecule and to synthesize molecules that bind the critical site (see Detailed Description of the Invention, page 6, line 24 - page 46, line 35). An attempt to incorporate specific details of each of the many possible procedures available in the art would be unduly burdensome and limit the scope of applicant's

invention to those specific embodiments disclosed. As indicated below, applicant's disclosure and the state of the art give more than enough guidance for the skilled practitioner to determine critical sites and the location of minor grooves in an RNA molecule, as well as synthesize the compounds designed by the methods of this invention.

For example, methods to determine whether a particular site on an RNA molecule is critical to function are well-known in the art and include anticodon substitution (see page 15, lines 5 - 24 and references therein), *in vivo* "transplantation assays" as devised by Normanly et al., *Nature, 321,* pp. 213-219 (1986) (see, page 15, line 25 - page 18, line 12), and use of altered, *in vitro* synthesized RNA molecules (see e.g., page 9, line 32-page 12, line 10, and the "mini-helix" substrate system (page 32, line 14 - page 34, line 19). Furthermore, as additional guidance, applicant discloses general strategies in which the above-mentioned methods may be used for identifying critical site nucleotides and associated structures in RNA (see page 42, line 19 - page 43, line 19).

The use of x-ray analysis is a well-known method to determine the tertiary features (such as the location of the minor groove) of RNA molecules and has been known in the art for over 15 years (see, e.g., Robertus et al., *Nature, 250*, pp. 546-551 (1974) (copy enclosed); Rich and Schimmel, *Nucl. Acids Res.*,

4, p. 1649-1665 (1977) (copy enclosed); and, in this application, see page 8, line 7 - page 9, line 2; page 18, line 13 - page 22, line 28). In addition, computer programs are readily available to the skilled practitioner for secondary and tertiary structure analysis (see page 37, line 3 - page 38, line 15; page 43, lines 13 - 16; and references therein).

Furthermore, numerous methods for the synthesis of organic compounds are known in the art (see, e.g., Rebek et al., *J. Am. Chem. Soc.*, 107, pp. 6736-6738 (1985); Rebek, *Science, 235*, pp. 1478-1484 (1987); Askew et al., *J. Am. Chem. Soc., 111*, pp. 1082-1090 (1989) (copies enclosed); and, in the specification, see page 38, line 16 - page 39, line 30). Applicant's disclosure and the state of the art, together, provide the skilled practitioner with more than sufficient guidance to carry out each step of the claimed methods and to synthesize the claimed compounds of this invention. Applicant cannot be expected to describe numerous possible syntheses nor to limit his invention to a few specific synthetic techniques.

The Examiner was also of the view that the Declaration of Dr. Paul R. Schimmel under 37 C.F.R. § 1.132, submitted with applicant's response of July 30, 1992, was merely applicant's opinion that one skilled in the art would know how to determine a critical site of function and minor groove in an RNA and how to design drugs. However, the declaration under 37 C.F.R. § 1.132

was not submitted as an opinion of an applicant, but the opinion of an **expert** on the state of the art and on the ability of one skilled in the art as of the filing date of this application. Dr. Schimmel's experience and contributions to the molecular and biochemical sciences (see paragraph 1 of the Schimmel declaration) make him eminently qualified to evaluate the state of the art as of the filing date of this application. The sworn declaration of Dr. Schimmel is that, at the time of filing of this application, one of skill in the art would have been able to determine the critical site of function in a targeted RNA molecule and the minor groove of the RNA molecule, and synthesize organic compounds using existing and routine techniques. See paragraph 4 of the Schimmel declaration of July 27, 1992.

The Examiner also cited three In re Hawkins cases (486 F.2d 569 (CCPA 1973); 486 F.2d 577 (CCPA 1973); 486 F.2d 579 (CCPA 1973)) as support for her view that methods for the determination of a critical site and minor grooves in RNA and methods for synthesis of compounds are "essential" and must be incorporated in detail into the application. However, the Hawkins cases are not applicable to applicant's case. In the Hawkins cases, the "essential" materials were starting compounds that were only disclosed in several pending British applications and were not otherwise available to the public or to the Patent Office (see e.g., 486 F.2d 569, 574; 486 F.2d 579, 580). This is

not the case in applicant's invention where the prior art contains a variety of well-known methods for the skilled practitioner to determine a critical site in an RNA molecule, to locate minor grooves in an RNA molecule, and to synthesize compounds. Thus, no essential material is unavailable or has been withheld for the practice of applicant's invention.

In view of the above comments, applicant request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112.

In view of all of the foregoing remarks, applicant requests that the Examiner withdraw the rejections of claims 1 and 3-19 and pass this application to allowance.

Respectfully submitted,

Jamie L. Greene
Reg. No. 32,467